MINI-REVIEW

Hypoxic Pulmonary Vasoconstriction and the Diffusing Capacity in Pulmonary Hypertension Secondary to Idiopathic Pulmonary Fibrosis

Seiichiro Sakao, MD, PhD; Nobuhiro Tanabe, MD, PhD; Koichiro Tatsumi, MD, PhD

Idiopathic pulmonary fibrosis (IPF) has a worse prognosis when complicated with pulmonary hypertension (PH). There are ≈3 million patients with IPF around the world,[1,2] and the prevalence rate of PH is 8.1% to 14.9%,[3] so there are ≈300 000 patients with IPF-PH. Moreover, the incidence rates of PH in patients with advanced and end-stage IPF are 30% to 50% and >60%, respectively.[4–6] Given that the diagnostic criteria of PH were changed from a mean pulmonary artery pressure (P_{PA}) of 25 to 20 mm Hg at the international conference in February 2018,[7] the number of patients with IPF-PH is expected to increase in the future.

Although pulmonary arterial hypertension (PAH)–approved drugs have been used in an attempt to treat IPF-PH, the outcomes were not good.[8] There is currently no evidence supporting the efficacy of such drugs for IPF-PH.[8] However, there are some patients with IPF-PH in whom PAH-approved drugs are actually effective,[9] and prospective studies to identify these patients are urgently needed for managing IPF-PH.

In this perspective article, we review the recent histopathological concepts of IPF-PH, especially focusing on a cohort of patients who were targeted for clinical trials and who had a mean P_{AP} of >25 mm Hg.

Why Are PAH-Approved Drugs Not Effective in Treating Patients With IPF-PH?

Although many patients with IPF-PH have only mild PH, some have severe PH, and their prognosis remains poor.[10] Single-agent clinical trials with sildenafil (STEP-IPF [the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis]),[11] bosentan (BUILD-3 [the randomized, placebo-controlled, Bosentan Use in Interstitial Lung Disease] trial),[12] ambrisentan (ARTEMIS-IPF [A Placebo-Controlled Trial Of Ambrisentan In Idiopathic Pulmonary Fibrosis]),[13] macitentan (MUSIC [Macitentan USe in an Idiopathic Pulmonary Fibrosis Clinical]),[14] and riociguat (RISE-IIP [Riociguat for the Treatment of Pulmonary Hypertension Associated With Idiopathic Interstitial Pneumonia])[15] have been conducted, but good results were not obtained. In the ARTEMIS-IPF and RISE-IIP trials, the disease progression was fast in the ambrisentan and riociguat groups; and because the hospitalization and mortality rates were also high, the trials were interrupted early. That happened because there is an IPF-PH–specific pathobiological cause behind it. The difference between PAH and IPF-PH depends on whether the increased P_{PA} is attributable to vasoconstrictive reactivity, primarily because of the PA itself or pulmonary vascular remodeling directly driven just by cytokines and growth factors[16] and/or in response to alveolar wall destruction and interstitial fibrosis.

Also, sudden changes in the disease state are difficult to predict and can be induced by various factors, and acute exacerbation occurs frequently. PH may be a risk factor associated with acute exacerbation in advanced IPF.[17] These previous findings suggest that it is necessary to formulate a protocol for clinical trials that controls these points.

Is PH a Necessary Evil in IPF-PH?

Alveolar hypoxia causes pulmonary vasoconstriction to divert blood flow away from hypoxic regions to well-ventilated areas to maintain the balance of ventilation/perfusion[18] (Figure 1) (Video S1). This is called hypoxic pulmonary vasoconstriction (HPV). The degree of blood flow from hypoxic to normoxic lungs by HPV depends on the following: (1) the magnitude of HPV and (2) the size of the hypoxic region.[18] When the alveolar hypoxic region is limited, HPV effectively achieves ventilation/perfusion matching by diverting the blood flow to the well-ventilated areas. In this state, there is no increase in the P_{PA}, as almost parts of the residual vascular bed are normal. However, as the alveolar hypoxic regions grow, blood flow diversion for ventilation/perfusion matching in all regions

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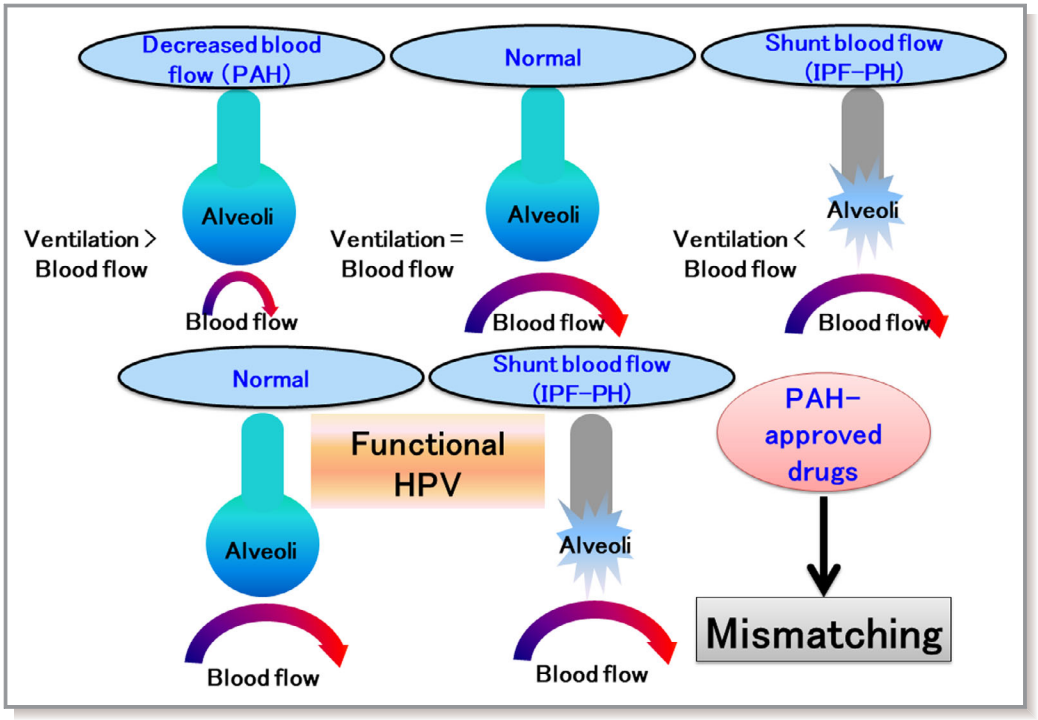

Figure 1. Hypoxic pulmonary vasoconstriction (HPV) and ventilation/perfusion matching. The ratio of ventilation/perfusion in normal subjects is almost equal. The ratio of ventilation/perfusion is increased in patients with pulmonary arterial hypertension (PAH) and decreased in patients with idiopathic pulmonary fibrosis–pulmonary hypertension (IPF-PH) (ie, shunt blood flow). In patients with IPF-PH, HPV diverts the blood flow away from hypoxic regions to well-ventilated areas to maintain the balance of ventilation/perfusion. If these patients were to be treated with PAH-approved drugs, the shunt blood flow would increase and induce ventilation/perfusion mismatching. See Video S1.

becomes difficult,[18] especially in the patients with severe alveolar wall destruction and interstitial fibrosis.[16]

In patients with IPF-PH, if the HPV functionally works for keeping ventilation/perfusion matching, it leads to maintaining oxygen tension. However, this likely comes at the price of an increased P_{PA}. In this sense, selective pulmonary vasodilators (ie, PAH-approved drugs) might destroy the physiological homeostasis controlled by the HPV function (Figure 1) (Video S1). Among these vasodilators, the phosphodiesterase type 5 inhibitor (PDE-5I) sildenafil has been shown to achieve selective pulmonary vasodilation and to maintain the homeostasis controlled by HPV in patients with severe lung fibrosis and severe PH (mean P_{PA} >35 mm Hg).[19] This suggested that vasodilators, including PDE-5Is and guanylate cyclase stimulators, which work through the NO/cGMP pathway, improve exercise tolerance and hemodynamics in patients with IPF-PH. Thus, controlled randomized trials were undertaken to confirm the effective roles of these drugs. The STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) is a double-blind, randomized, placebo-controlled trial of sildenafil in patients with severe IPF and PH.[11] Although the differences in the secondary end points, including arterial oxygenation, carbon monoxide (CO) diffusion capacity, degree of dyspnea, and quality of life, were significant, there was no significant difference in the 6-minute walk distance as the primary end point.[11] As shown above, the RISE-IIP trial was interrupted early because of increased serious adverse events and mortality.[15]

HPV might, therefore, be a necessary evil and should be dealt with carefully. However, continuous HPV-related vasoconstriction can induce shear stress–related vascular remodeling,[20] eventually leading to an increase in the P_{PA}. As mentioned above, HPV may be a necessary evil, especially in the cohorts in which HPV functionally works, but it can also result in a vicious cycle and cannot be allowed to go unchecked.

In patients with IPF-PH with almost the same pulmonary functional disorder, what is the difference between the patients who do and do not develop PH? It should be attributable to pulmonary vascular remodeling directly driven just by cytokines and growth factors[16] and, moreover, may be attributable to the magnitude of functional HPV in accordance with the degree of the hypoxic region and the degree of vasoconstrictive reactivity that is primarily caused by the PA

itself, like PAH. In patients with IPF-PH, it may be necessary to determine whether vasoconstrictive reactivity is primarily caused by the PA itself or HPV.

However, the numerous studies have demonstrated the absence of a correlation between the forced vital capacity[10,21,22] or the extent of lung fibrosis[23] and the mean P_{PA}. In patients with IPF-PH, "the size of the hypoxic region" and "the size of the fibrotic region" would have almost the same meaning. In patients with IPF-PH with symptoms that are not sufficiently explained by respiratory dysfunction alone (ie, with mild lung parenchymal abnormalities and severe PH), vasoconstrictive reactivity, primarily caused by the PA itself, may be predominant. Moreover, in addition to vasoconstrictive reactivity, other potential mechanisms for the increase in P_{PA} should be considered. Actually, pulmonary vascular remodeling that is directly driven just by cytokines and growth factors has been suggested to have a relevant role in the progress of PH, the same as vasoconstrictive reactivity.[16,24]

Is Vasoconstrictive Reactivity Primarily Caused by the PA Itself or HPV?

A recent study demonstrated that the protein expression of Janus kinase 2, which is a nonreceptor tyrosine kinase, was upregulated in the lung tissue, including the PAs of patients with IPF.[25,26] Janus kinase 2 induces epithelial-to-mesenchymal and fibroblast-to-myofibroblast transitions and, moreover, leads to the vasoconstriction of small PAs through the large-conductance calcium-activated potassium channels. It was hypothesized that Janus kinase 2 plays a critical role in the vasoconstriction of PAs in patients with IPF. The Janus kinase 2 expression in the PAs may also predict the magnitude of vasoconstrictive reactivity that is primarily caused by the PA itself.

Recently, a regulatory subunit of NADPH (Nicotinamide Adenine Dinucleotide Phosphate Reduced Form) oxidases, p22phox, was indicated to be associated with HPV and to play a role in ventilation/perfusion matching in patients with chronic obstructive pulmonary disease.[27] Although no studies have supported the potential role of p22phox in patients with IPF, we discuss p22phox as a potential biomarker for HPV. In $p22phox^{-/-}$ mice under conditions of chronic hypoxia, HPV cannot function, leading to a significant amelioration in right ventricular dysfunction and PA remodeling.[27] In patients with chronic obstructive pulmonary disease, the p22phox expression was shown to be significantly lower than in controls, but the patients with a preserved expression of p22phox had a higher P_{PA} and better oxygenation ratio (PaO_2/FiO_2 ratio: the ratio of arterial oxygen partial pressure to fractional inspired oxygen) than the patients with a low expression of p22phox, suggesting that HPV functioned as a necessary evil for maintaining better oxygen tension, but as the price it led to PH. NADPH oxidase has been acknowledged as a hypoxic sensor for HPV and is known to have an important role in HPV.[28] According to previous studies, HPV is biphasic, demonstrating a short-term phase (within seconds) and a sustained phase (several hours).[18] The p22phox has been shown to be involved in only the sustained phase,[28] in which the rho-rho Do not change kinase signaling pathway is likely activated and which is dependent on the endothelial cell function.[29,30] Although whether p22phox functions the same way in patients with IPF-PH and chronic obstructive pulmonary disease is unclear, the p22phox expression may predict the magnitude of functional HPV in these patients.

The Diffusing Capacity of the Lungs for CO in Patients With IPF-PH

Considering the pathophysiological characteristics of IPF-PH, it is also necessary to keep in mind the impairment of the diffusing capacity of the lungs for CO (DL_{CO}). A low capacity of DL_{CO} has been shown to relate to PH development in patients with IPF.[22] The DL_{CO} reflects the gas-diffusing ability for transferring CO from inhaled air to hemoglobin in the alveolar capillary membrane.[31,32] DL_{CO} means a physical process in that oxygen travels from the alveolar space to the red blood cell hemoglobin. In this process, oxygen passes through alveolar epithelial cells, lung interstitium, capillary endothelial cells, plasma, and erythrocyte membranes and eventually reaches hemoglobin. A decrease in the diffusion capacity is a pathological condition in which certain disorders occur in this process, such as alveolar membrane disorder/thickening (eg, IPF), loss of alveolar area (eg, chronic obstructive pulmonary disease), pulmonary capillary blood volume reduction (PAH or stenosis/occlusion of the PA caused by chronic thromboembolic PH), and a reduction in the hemoglobin concentration in the blood (eg, anemia). In patients with PAH, the primary cause of a low DL_{CO} is a reduction in the pulmonary capillary blood volume, whereas in patients with IPF-PH, disorder/thickening of the alveolar to capillary membrane reduces the DL_{CO} (Figure 2) (Video S2). Even if PAH-approved drugs improve the pulmonary capillary blood volume, a low DL_{CO} caused by lesions from the alveolar to the capillary membrane will persist in patients with IPF-PH, resulting in little likelihood of the oxygenation improving (Figure 2) (Video S2). Moreover, occlusive venopathy has also been demonstrated in nonfibrotic lung areas of patients with IPF,[33] suggesting that pulmonary capillary blood volume reduction caused by occlusive venopathy is also related to low DL_{CO} values in patients with IPF-PH.

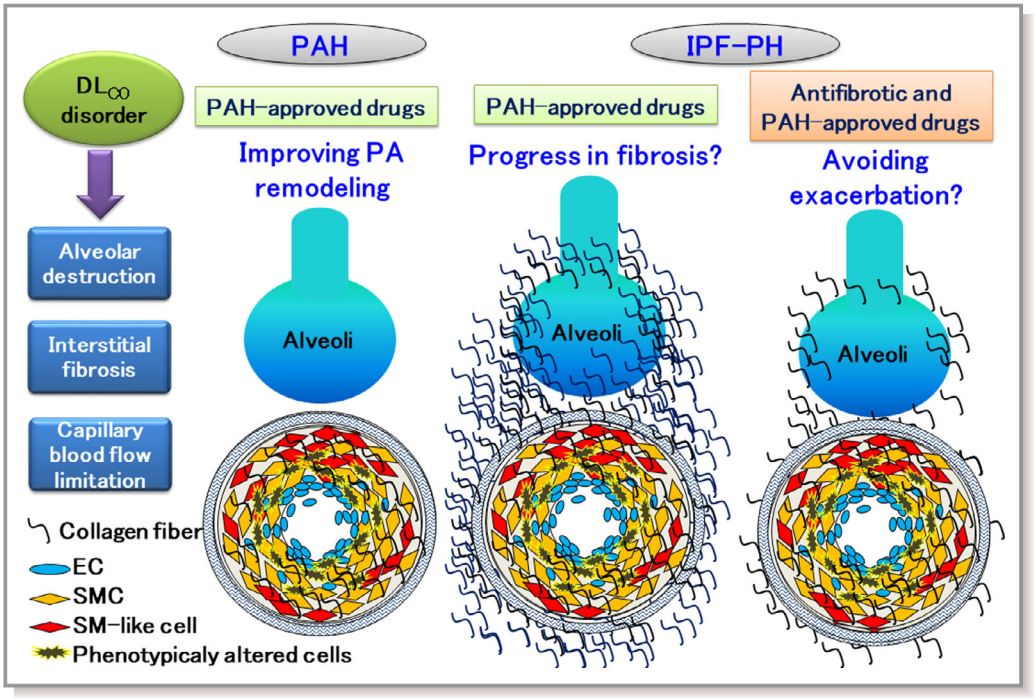

Figure 2. The diffusing capacity of the lungs for carbon monoxide (DL_{CO}) and pulmonary arterial hypertension (PAH)–approved drugs in patients with idiopathic pulmonary fibrosis–pulmonary hypertension (IPF-PH). A decrease in the diffusion capacity is a pathological condition in which certain disorders occur in this process, such as alveolar membrane disorder/thickening, loss of alveolar area, pulmonary capillary blood volume reduction, and a reduction in the hemoglobin concentration in the blood. In patients with PAH, the primary cause of a low DL_{CO} is a reduction in the pulmonary capillary blood volume, whereas in patients with IPF- PH, disorder/thickening of the alveolar to capillary membrane reduces the DL_{CO}. Even if the pulmonary capillary blood volume improves with PAH-approved drugs, a low DL_{CO} caused by lesions from the alveolar to capillary membrane will persist in patients with IPF-PH, resulting in little likelihood of the oxygenation improving. Therefore, to improve DL_{CO}, it is necessary to improve the interstitial changes as well or at the least maintain the state of interstitial alterations and avoid acute exacerbation. See Video S2. EC indicates endothelial cell; PA, pulmonary artery; SM, smooth muscle; SMC, SM cell.

Therefore, to improve DL_{CO}, it is necessary to improve the interstitial changes as well or at the least maintain the state of interstitial alterations and avoid acute exacerbation (Figure 2) (Video S2). However, sudden changes in the disease state are difficult to predict and can be induced by various factors, and acute exacerbation occurs frequently. PH may be a risk factor associated with acute exacerbation in advanced IPF.[17] These previous findings suggest that it is necessary to control the activity of interstitial fibrosis during IPF-PH treatment.

Future Concepts

As shown above, when treating patients with IPF-PH, it is necessary to consider a protocol that controls not only PH but also interstitial lesions to avoid acute exacerbation of IPF (Figure 2) (Video S2). Combination therapy with antifibrotic drugs and PAH-approved drugs has been attempted in IPF. However, the combined use of a PDE-5I and the antifibrotic agent nintedanib failed to show much efficacy,[34] possibly caused, in part, by cases being registered in the study regardless of the presence of PH.

Because PDE-5Is and soluble guanylate cyclase stimulators are not expected to exacerbate ventilation/perfusion mismatch,[35] many trials have been conducted using PDE-5Is or soluble guanylate cyclase stimulators on IPF-PH,[8] but promising results have not been obtained. It is generally believed that parenteral prostaglandin I2 exacerbates ventilation/perfusion mismatch.[35] However, as in the article by Saggar et al, if the dose of parenteral prostaglandin I2 can be finely adjusted, it also can be effective to decrease P_{PA} without deterioration of ventilation/perfusion mismatch.[36] Given that trials of single agents have not shown marked therapeutic efficacy, future studies may need to confirm the safety and efficacy of PAH-approved drugs in combination with antifibrotic drugs. It is also necessary to conduct randomized clinical trials that will provide evidence supporting the proper use of PAH-approved drugs. Searching for biomarkers that determine whether vasoconstrictive

reactivity is primarily caused by the PA itself or HPV is also crucial as a future prospect. As shown above, the regulatory subunit of NADPH oxidase, p22phox, plays an essential role in HPV,[27] and its expression has been shown to be related to functional HPV, suggesting that p22phox may be useful as a biomarker for predicting the degree of HPV in patients with IPF-PH.

To avoid ventilation/perfusion mismatch, it may be necessary to develop an appropriate drug delivery system, such as that using an inhalation device. On that note, phase 2 and 3 trials of inhaled treprostinil in PH with interstitial lung disease are currently ongoing (Clinical Trial.gov; https://clinicaltrials.gov/ct2/show/study/NCT02630316).

There is currently no way to differentiate the boundary between patients with IPF-PH for whom PAH-approved drugs are effective roles and those for whom these drugs are ineffective. However, in an actual clinical setting, PAH-approved drugs may be expected to be effective if patients with IPF-PH have vasoconstrictive reactivity, primarily caused by the PA itself, like PAH. It will likely be necessary to seek ways to differentiate these patients to identify the group indicated for therapy with PAH-approved drugs among total patients with IPF-PH, leading to the further development of new treatment strategies for IPF-PH.

Author Contributions

Dr Sakao conceived of the report, contributed to its design and conception, and drafted the manuscript. Drs Tanabe and Tatsumi contributed to the report design and drafted the manuscript. All authors read and approved the final manuscript.

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Key Words: diffusing capacity of the lungs for carbon monoxide • hypoxic pulmonary vasoconstriction • idiopathic pulmonary fibrosis • pulmonary hypertension

SUPPLEMENTAL MATERIAL

Supplemental Video Legends:

Video S1. Hypoxic pulmonary vasoconstriction (HPV) and $\dot{V}_A/\dot{Q}$ matching. The ratio of ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}$) in normal subjects is almost equal. The ratio of $\dot{V}_A/\dot{Q}$ is increased in patients with PAH and decreased in patients with IPF-PH, i.e. shunt blood flow. In IPF-PH patients, HPV diverts the blood flow away from hypoxic regions to well-ventilated areas in order to maintain the balance of $\dot{V}A/\dot{Q}$. If these patients were to be treated with PAH-approved drugs, the shunt blood flow would increase and induce $\dot{V}A/\dot{Q}$ mismatching. PAH indicates pulmonary arterial hypertension; PH, pulmonary hypertension; IPF, idiopathic pulmonary fibrosis; HPV, hypoxic pulmonary vasoconstriction. Best viewed with Windows Media Player.

Video S2. The diffusing capacity of the lungs for carbon monoxide (DL_{CO}) and PAH-approved drugs in patients with IPF-PH. A decrease in the diffusion capacity is a pathological condition in which certain disorders occur in this process, such as alveolar membrane disorder/thickening, loss of alveolar area, pulmonary capillary blood volume reduction, and a reduction in the hemoglobin concentration in the blood. In patients with PAH, the primary cause of a low DL_{CO} is a reduction in the pulmonary capillary blood volume, whereas in patients with IPF- PH, disorder/thickening of the alveolar to capillary membrane reduces the DL_{CO}. Even if the pulmonary capillary blood volume improves with PAH-approved drugs, a low DL_{CO} due to lesions from the alveolar to capillary membrane will persist in patients with IPF-PH, resulting in little likelihood of the oxygenation improving. Therefore, in order to improve DL_{CO}, it is necessary to improve the interstitial changes as well or at the very least maintain the state of interstitial alterations and avoid acute exacerbation. PAH indicates pulmonary arterial hypertension; PH, pulmonary hypertension; IPF, idiopathic pulmonary fibrosis; DL_{CO}, the diffusing capacity of the lungs for carbon monoxide; PA, pulmonary artery; EC, endothelial cell; SMC, smooth muscle cell. Best viewed with Windows Media Player.